At the recent meeting of the Cell Transplantation Society in Miami, the long-running disagreement between the majority of researchers working on myoblast transplantation and the group of Dr. Law was brought up again but not resolved. Unfortunately, this impasse is not just a matter of inconvenience for scientists, for whom patience is part of the job. It is far more serious for Duchenne dystrophy patients and their families, who suffer widespread confusion because neither they nor the majority of scientists are able to judge the validity or otherwise of Dr. Law's claims of the beneficial effects of his treatments. The patients cannot afford delay. In view of this, we feel that it is proper to air publicly the nature of the doubts felt by the majority of scientists and clinicians who have experience in myoblast transplantation and to lay out a basis for resolution of the most critical area of dispute.

Our doubts arise mainly from what we perceive as deficiencies in the nature or quality of the evidence presented by Dr. Law's group over the past few years as to the success of the procedures he is performing. Fortunately, the main issue, outlined below, could be validated simply and speedily, so we are able to make a reasonable proposal encompassing what we would consider to be the minimum requirements to satisfy our scepticism.

EVIDENCE OF PERSISTENCE OF DONOR-DERIVED MUSCLE

The majority of workers on human myoblast transplantation have found little or no evidence of donor dystrophin resulting from myoblast implantation, even when the donor and recipient were well matched at the major histocompatibility locus and maintained on immunosuppressive therapy (3,5,9,14,15). Careful studies have identified evidence of both a humoral and cellular immune response against donor antigens (6-8,10,13). This is backed up by extensive work in mice showing that donor-derived myoblasts and muscle fibers are rapidly rejected on the basis of major histocompatibility mismatches and also as a consequence of minor antigen mismatches (1,2,17). In contrast, Dr. Law reports success with grafts from nonsibling, sometimes unrelated, donors, and withdraws Cyclosporin immunosuppression after 6 months (11-13). Evidence of formation and survival of significant amounts of donor-derived muscle is therefore crucial to Dr. Law's case and is the major area in which there are concrete disparities between his reports and those of others who have performed human studies.

UNEQUIVOCAL EVIDENCE OF DONOR MYOBLASTS

The evidence provided so far to support Dr. Law's claim that donor cells do survive is the presence of dystrophin-positive fibers in biopsies taken from muscles of patients up to 6 years after transplantation. This evidence is inadequate for two reasons.
1. Many DMD patients' muscles contain sporadic groups of so called 'revertant fibers' (16), which contain more or less normal levels of dystrophin when stained with a polyclonal antidystrophin antibody of the type used by Dr. Law (12). The nature of these fibers is uncertain, but they do occur with very variable frequency and they become more conspicuous in both size of cluster and in apparent frequency with increasing age. In mdx mice, they also appear more frequently in injected muscles, even sham-injected muscles, than in noninjected muscles (4).

Irrefutable evidence for survival of muscle derived from donor myoblasts could readily be obtained from some of the patients in Dr. Law's experimental series by selecting those in whom there is an absence of certain commonly deleted exons. Biopsies from these could be immunostained with a panel of monoclonal antibodies that specifically recognize parts of dystrophin encoded by the exons that the patient lacks. It is generally accepted that fibers stained with these antibodies could only have been derived from the grafted cells because they contain parts of dystrophin that the patient's own cells cannot synthesize (14).

2. Immunofluorescence data shown by Dr. Law in Miami was uninformative in that there was no indication of the frequency of the dystrophin positive fibers within the biopsies: all of the photomicrographs were at too high a power to give any overall indication of
this parameter. The whole rationale of myoblast transfer is that the donor cells would provide sufficient amounts of the missing gene product, dystrophin, to rectify the functional defect in a significant proportion of the recipient patient's muscles. So, quantitative assessment of the numbers of dystrophin-positive fibers is an important factor to be evaluated if Dr. Law is to validate his claims. It is also important to determine the frequency with which successful transplantation occurs in patients.

We suggest that the whole problem could easily be cleared up to everyone's satisfaction if Dr. Law were to agree to an independent organizer collating and sending out samples of biopsy material from selected patients, together with positive and negative controls, to independent laboratories for blind assessment. This would be a study of defined scope, for it would only involve patients in whom deletions of suitable exons had been identified and so confirmatory evidence of Dr. Law's claims could quickly be obtained. We appreciate that the development of a successful therapeutic procedure is seldom achieved at a single stroke, and we would be impressed by the demonstration of even a significant improvement in the success rate in Dr. Law's series as compared with those of other groups who have attempted human myoblast transplantation. So important is the outcome of such an assessment to patients and their families that major national charities concerned with neuromuscular diseases have indicated that they would agree to underwrite the cost of such an operation. and we are sure that a mutually acceptable independent organizer could quickly be appointed.

On the basis of present evidence we, the undersigned, try to discourage families of DMD patients from submitting their sons to Dr. Law's protocols. However, if it could be established that he does indeed have an effective protocol for myoblast transplantation, then it would be to everyone's benefit that it be widely known and supported by other scientists in the field. Under such circumstances, there would be widespread encouragement of patients to enter this trial therapy and Muscular Dystrophy Research organizations would be keen to fund Dr. Law to further the development of his procedures and spread their benefits to more patients.

We await a positive response from Dr. Law with eager anticipation.


REFERENCES

Seven years ago, when I began myoblast transfers ("MTT") in human subjects, there was great concern among some that the procedure would not be safe. Indeed, the number of articles on the subject of MTT safety are legion.

It is with pleasure that I can report to you today that Cell Therapy Research Foundation has transplanted well over 100 human subjects—many of them with 25 billion or 50 billion cells—with a 100% record of safety. I believe that the understandable concerns regarding safety have been forever put to rest.

It would appear that many of these same scientists are today questioning the efficacy of MTT. In particular, I refer you to the letter from Partridge et al., which is published in this issue.

I am equally pleased to be able to tell you that the results of MTT have thus far been very encouraging—particularly the 50 billion cell transfers. I hope to be invited to submit a paper to your Journal for publication 1 yr from this edition putting to rest forever the question of efficacy. In the meantime, we are continuing our work with very good results and look forward to the exchange of ideas with all scientists interested in gene therapy with a view to ameliorating, if not curing, Duchenne muscular dystrophy.

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